PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Michael J. Breslin, *et. al*		
Serial No.:	10/506,702	Case No. 21047YP	Art Unit: 1626
Filed:	September 07, 2004		
For:	MITOTIC KINESIN INHIBITORS		Examiner: R. Havlin

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF CHRISTOPHER D. COX, PhD

Sir:

I Christopher D. Cox, PhD.,

do hereby declare that

1. I am employed by Merck & Co., Inc as a Senior Research Fellow in the department of Medicinal Chemistry. My *curriculum vitae* is attached as Exhibit 1.

2. My responsibilities at Merck & Co., Inc. include basic oncology research. I worked extensively on the discovery of mitotic kinesin inhibitors. During the course of that work, my team and I discovered many mitotic kinesin inhibitors, including those claimed in the instant application.

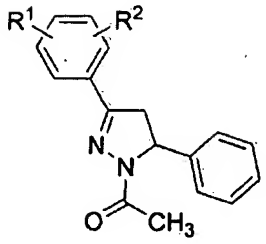
3. The compounds of the instant invention are 2,5-difluoro substituted 4,5-dihydro pyrazoles. The 2,5 difluoro substitution on the 3-phenyl unexpectedly results in a

favorable profile when compared to mono-fluorinated and other di-fluorinated analogues. The 2,5-difluoro compounds are very potent inhibitors of kinesin spindle protein (hereinafter "KSP").

The original HTS lead we discovered from screening our sample collection identified compound **A** with a 2-chloro substituent as a promising lead. We walked the chlorine to the 3- and 4-positions and noted a moderate loss in potency for the 3-position and a dramatic loss for the 4-position (compounds **B** and **C**). We interpreted the data to mean that 2- and 3-substitution were best, and 4-susbtitution was poor. We then changed the 2-Cl to a 2-F (compound **D**) and noticed similar potency, but since fluorine is less greasy and more compatible with optimal drug properties, we focused on fluoro substitution for our remaining analogues. Holding the fluorine in the 2-position constant, we added fluorines at the other positions that were optimal, specifically the 3-, 5- and 6 positions (note: by 3-, 4-, and 6-, I am assuming that the ring can rotate within our reference frame such that 2-subsitiution is the same as 6-substitution, 3- is the same as 5-, etc., but they are numbered differently when there is more than one substituent on the ring). What we noticed, quite unexpectedly, was that the 2,5-disubustitution yielded the most potent compound, indicating that in our original SAR study, it really was not the "3-position" that was good, but rather the "5-position" (compare compounds **E** and **G**). The 3,4-difluoro compound **H** was never made based on the lack of potency in compound **C** – I would expect this compound to have a potency of > 10,000 nM.

Table 1 summarizes the data described above:

Table 1.



Compound	R^1	R^2	ATPase (nM)
A	2-Cl	H	3,900
B	3-Cl	H	9,800
C	4-Cl	H	> 50,000
D	2-F	H	3,600
E	2-F	3-F	12,700
F	2-F	6-F	10,900
G	2-F	5-F	94
H	3-F	4-F	not made

4. These results were unexpected, and said results were realized prior to the filing date of the above-captioned application.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 or Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Christopher D. Cox, PhD

27-May-2009

Date

EXHIBIT 1

DECEMBER 2008

CURRICULUM VITAE

I. PERSONAL

Christopher Cox, Ph. D.
422 Hoffman Road
Harleysville, PA 19438
(267) 210-3474

II. EDUCATION

Johns Hopkins University, Baltimore, MD Organic Chemistry Ph. D.	1999
Towson State University, Towson, MD Chemistry B. S. Summa Cum Laude	1994

III MERCK/MRL EMPLOYMENT HISTORY

Medicinal Chemistry

Sr. Research Chemist	11/2001 - 9/2004
Research Fellow	10/2004 – 3/2008
Sr. Research Fellow	4/2008 - Present

IV. NON-MERCK EMPLOYMENT HISTORY

V. ACADEMIC EXPERIENCE

NIH Postdoctoral Fellow	Columbia University, New York, NY	1999 - 2001
Graduate Student	Johns Hopkins University, Baltimore, MD	1994 - 1999
Undergrad. Res. Asst.	Towson State U., Towson, MD	1994
NSF-REU Fellow	University of Maryland, College Park, MD	1993

VI. TRAINING

VII. SOCIETY MEMBERSHIPS

Sigma Xi Member
American Chemical Society

VIII. ACADEMIC AND PROFESSIONAL HONORS

NIH Postdoctoral Fellowship	1999
Kilpatrick Graduate Fellowship	1998
ACS, Div. Of Organic Chem., Graduate Fellowship	1997
Ernest M. Marks Fellowship	1997
ACS, MD Section, Outstanding Student Award	1994
NSF-REU Fellowship	1993
Merck Index Achievement Award in Organic Chem.	1992

IX. PUBLICATIONS AND PATENTS

PUBLICATIONS

1. "Brazilian Baccharis Toxins: Livestock Poisoning and the Isolation of Macrocyclic Trichothecene Glucosides."
   B. Jarvis, S. Wang, C. Cox, M. Rao, V. Philip, M. Varaschin, C. Barros
   Natural Toxins **1996**, 4, 58-71.

2. "Copper(II)-Catalyzed Amide Isomerization: Evidence for N-Coordination."
   C. Cox, D. Ferraris, N. N. Murthy, T. Lectka
   J. Am. Chem. Soc. **1996**, 118, 5332-5333

3. "Crystal Structure and Triboluminescence 2. 9-Anthracenecarboxylic Acid and its Esters."
   L. Sweeting, A. Rheingold, J. Gingerich, A. Rutter, R. Spence, C. Cox, T. Kim
   Chem. Mater. **1997**, 9, 1103-1115.

4. "Intramolecular Catalysis of Amide Isomerization."
   C. Cox, V. G. Young Jr., T. Lectka
   J. Am. Chem. Soc. **1997**, 119, 2307-2308.

5. "Solvent Effects on the Barrier to Rotation in Carbamates."
   C. Cox, T. Lectka
   J. Org. Chem. **1998**, 63, 2426-2427.

6. "Orthogonal" Lewis Acids: Catalyzed Ring Opening and Rearrangement of Acyl Aziridines."
   D. Ferraris, W. J. Drury III, C. Cox, T. Lectka
   J. Org. Chem. **1998**, 63, 4568-4569

PUBLICATIONS (continued)

7. "Intramolecular Catalysis of Amide Isomerization: Kinetic Consequences of the 5-NH--N_a Interaction in Prolyl Peptides."
C. Cox, T. Lectka
J. Am. Chem. Soc. **1998**, 120, 10660-10668.

8. "Diastereo- and Enantioselective Alkylation of α-Imino Esters with Enol Silanes catalyzed by R-Tol-BINAP-$CuClO_4$•$(MeCN)_2$."
D. Ferraris, B. Young, C. Cox, W. J. Drury III, T. Dudding, T. Lectka
J. Org. Chem. **1998**, 63, 6090-6091.

9. "A Novel Synthesis of α-Amino Acid Derivatives through Catalytic Enantioselective Ene Reactions of α-Imino Esters."
W. J. Drury III, D. Ferraris, C. Cox, B. Young, T. Lectka
J. Am. Chem. Soc. **1998**, 120, 11006-11007.

10. "Strong Hydrogen Bonding to the Amide Nitrogen of an "Amide Proton Sponge": Consequences for Structure and Reactivity."
C. Cox, H. Wack, T. Lectka
Angew. Chem., Int. Ed. Engl. **1999**, 38, 798-800.

11. "Nucleophilic Catalysis of Amide Isomerization."
C. Cox, H. Wack, T. Lectka
J. Am. Chem. Soc. **1999**, 121, 7963-7964.

12. "Intramolecular Acid-Catalyzed Amide Isomerization."
C. Cox, T. Lectka
Org. Lett. **1999**, 1, 749-752.

13. "Synthetic Catalysis of Amide Isomerization."
C. Cox, T. Lectka
Acc. Chem. Res. **2000**, 33, 849-858.

14. "Synthesis of the Functionalized Tricyclic Core of Lactonamycin by Oxidative Dearomatization."
C. Cox, S. J. Danishefsky
Org. Lett. 2000, 2, 3493-3496.

15. "Concise Synthesis of a Lactonamycin Model System by Diastereoselective Dihydroxylation of a Highly Fuctionalized Naphthoquinone."
C. Cox, S. Danishefsky
Org. Lett. **2001**, *3*, 2899-2902.

PUBLICATIONS (continued)

16. "Catalytic, Enatioselective Alkylation of α-Imino Esters: The Synthesis of Nonnatural α-Amino Acid Derivatives."
D. Ferraris, B. Young, C. Cox, T. Dudding, W. Drury III, L. Ryzhkov, A. Taggi, T. Lectka
J. Am. Chem. Soc. **2002**, *124*, 67-77.

17. "Studies Directed Toward the Total Synthesis of Lactonamycin: Control of the Sense of Cycloaddition of a Quinine Through Directed Intramolecular Catalysis."
C. Cox, T. Siu, S. Danishefsky
Angew. Chem., Int. Ed. Engl. **2003**, *42*, 5625-5629.

18. "Total Synthesis of Lactonamycinone."
T. Siu, C. Cox, S. Danishefsky
Angew. Chem., Int. Ed. Engl. **2003**, *42*, 5629-5634.

19. "Two-Step Synthesis of β-Alkylchalcones and Their Use in the Synthesis of 3,5-Diaryl-5-Alkyl-4,5-Dihydropyrazoles."
C. Cox, M. Breslin, B. Mariano
Tetrahedron Lett. **2004**, *45*, 1489-1493.

20. "Kinesin Spindle Protein (KSP) Inhibitors. Part 1: The Discovery of 3,5-diaryl-4,5-dihydropyrazoles as Potent and Selective Inhibitors of the Mitotic Kinesin KSP."
C. Cox; M.J. Breslin; B.J. Mariano; P.J. Coleman; C.A. Buser; E.S. Walsh; K. Hamilton; H.E. Huber; N.E. Kohl; M. Torrent; Y. Yan; L.C. Kuo; G.D. Hartman
Bioorg. & Med. Chem. Lett. **2005**, *15*, 2041-2045.

21. "Kinesin Spindle Protein (KSP) Inhibitors. Part 4:[1] Structure-based Design of 5-alkylamino-3,5-diaryl-4,5-dihydropyrazoles as Potent, Water-soluble Inhibitors of the Mitotic Kinesin KSP."
C. Cox; M. Torrent, M.J. Breslin; B.J. Mariano; D.B. Whitman, P.J. Coleman; C.A. Buser; E.S. Walsh; K. Hamilton; M.D. Schaber, R.B. Lobell, W. Tao, V.J. South; N.E. Kohl; Y. Yan; L.C. Kuo; T. Prueksaritanont; D.E. Slaughter; C.Li; E. Mahan; B. Lu; G.D. Hartman
Bioorg. & Med. Chem. Lett. **2006**, *16*, 3175-3179.

PUBLICATIONS (continued)

22. "Kinesin Spindle Protein (KSP) Inhibitors. Part V: Discovery of 2-Propylamino-2,4-Diaryl-2,5-Dihydropyrroles as Potent, Water-Soluble KSP Inhibitors, and Modulation of their Basicity by β-Fluorination to Overcome Cellular Efflux by P-Glycoprotein."
C. Cox; M.J. Breslin; D.B. Whitman, P.J. Coleman; R.M. Garbaccio; M.E. Fraley; M.M. Zrada; C.A. Buser; E. S. Walsh; K. Hamilton; R. B. Lobell, W. Tao; M.T. Abrams; V.J. South; H.E. Huber; N.E. Kohl, G.D. Hartman.
Bioorg. & Med. Chem. Lett. **17**, 2697-2702 (2007).

23. " Kinesin spindle protein (KSP) inhibitors. Part 6: Design and synthesis of 3,5-diaryl-4,5-dihydropyrazole amides as potent inhibitors of the mitotic kinesin KSP."
Coleman, Paul J.; Schreier, John D.; Cox, Christopher D.; Fraley, Mark E.; Garbaccio, Robert M.; Buser, Carolyn A.; Walsh, Eileen S.; Hamilton, Kelly; Lobell, Robert B.; Rickert, Keith; Tao, Weikang; Diehl, Ronald E.; South, Vicki J.; Davide, Joseph P.; Kohl, Nancy E.; Yan, Youwei; Kuo, Lawrence; Prueksaritanont, Thomayant; Li, Chunze; Mahan, Elizabeth A.; Fernandez-Metzler, Carmen; Salata, Joseph J.; Hartman, George D.
Bioorganic & Medicinal Chemistry Letters , **17**(19), 5390-5395. (2007)

24. "Kinesin Spindle Protein (KSP) Inhibitors. 9. Discovery of (2*S*)-4-(2,5-Difluorophenyl)-*N*-[3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (MK-0731) for the Treatment of Taxane-Refractory Cancer."
C.D. Cox, P.J. Coleman, M.J. Breslin, D.B. Whitman, R.M. Garbaccio, M.E. Fraley...Y. Yan, ...G.D. Hartman
J. Med. Chem., **51**, 4239-4252, (2008)

X. OTHER ACCOMPLISHMENTS

INVITED LECTURES

1. "Discovery of L-001154704: A Potent and Selective Inhibitor of the Mitotic Kinesin KSP".
Merck Chemistry Council Conference, La Sapiniere, Quebec - Canada
August 2004

2. "Intramolecular Catalysis of Amide Isomerization and its Role in Protein Folding".
Towson State University, Towson, MD
May 1998.

INVITED LECTURES (continued)

3. " Discovery of Kinesin Spindle Protein Inhibitor MK-0731 for the Treatment of Taxane-Refractory Cancer".
   Johns Hopkins University
   April 30, 2008:

PRESENTATIONS

1. "Discovery and optimization of kinesin spindle protein (KSP) inhibitors."
   Cox, Christopher D.; Coleman, Paul J.; Fraley, Mark E.; Garbaccio, Robert M.; Breslin, Michael J.; Whitman, David B.; Schreier, John D.; Hartman, George D.; Torrent, Maricel; Lobell, Rob; Buser, Carolyn; Tao, Weikang; Huber, Hans; Kohl, Nancy E.; Yan, Youwei; Kuo, Lawrence C.
   Abstracts of Papers, *233rd ACS National Meeting*, Chicago, IL, United States, March 25-29, 2007 (2007), MEDI-211.

2. "HTS to MK-0731: The Role of Fluorine in Optimization of Kinesin Spindle Protein (KSP) Inhibitors for the Treatment of Cancer."
   Spring ACS National Meeting, April 7, 2008 (2008)

3. "Chemical Strategies to Alter P-Glycoprotein Efflux of Drug Molecules"
   Spring ACS National Meeting, April 8, 2008 (2008)